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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,262	04/05/2005	Masahiko Koike	084437-0172	4696

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
WELTER, RACHAEL E	

ART UNIT	PAPER NUMBER
4131	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,262	KOIKE ET AL.	
	Examiner	Art Unit	
	RACHAEL WELTER	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :7/13/05,8/31/06,10/26/06,11/20/07 .

DETAILED ACTION

Acknowledgments

The Examiner acknowledges receipt of the preliminary amendment filed 4/5/05 wherein the specification was amended to insert a reference to conform to accepted US Patent Prosecution practice.

Note: Claims 1-14 are pending.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. No English translation of the Certified Copy of the Foreign Priority Application has been received.

Information Disclosure Statements

The information disclosure statements (IDS) submitted on July 13, 2005, August 31, 2006, October 26, 2006, and November 20, 2007 were in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. A signed copy of forms 1449 are enclosed herewith.

Specification

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 7, and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The four claims all have the phrase "except

insulin sensitizers" in parentheses. In this format, it is not clear whether the phrase within parentheses is a required claim limitation. Appropriate correction is required.

In addition, claims 4 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Presently, the ratio of median size between the insulin sensitizer and active ingredient and the ratio of median size between pioglitazone hydrochloride and metformin hydrochloride is unclear. For purposes of examining, the examiner has interpreted the claim as having a ratio of active ingredient median size to an insulin sensitizer median size of 0.5 to 15.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Lilliott et al (WO 01/35941).

Claims 1-3, 7-12 are drawn to a solid preparation having an insulin sensitizer and an active ingredient that are uniformly dispersed. The active ingredient is preferably a biguanide that is metformin hydrochloride. Further limitations of the solid preparation include having a specific hardness, a coefficient of variation of the insulin sensitizer

content, and properties exhibited during a dissolution test according to the Paddle Method.

Lilliott et al teach a pharmaceutical composition comprising an insulin sensitizer, thiazolidinedione, and metformin hydrochloride (abstract). According to Lilliott et al, a suitable formulation is a tablet formulation (pg. 3, line 6). In addition, Lilliott et al refer to uniformly dispersed active ingredients in the composition when the prior art describes a composition comprising thiazolidinedione and its carrier in a homogenous admixture with metformin hydrochloride and its carrier (Claim 4). However, Lilliott et al does not teach a solid preparation with a hardness of 100-400N, a coefficient of variation of the insulin sensitizer content equal to less than 6%, and an elution of more than 70% of insulin sensitizer at 30 minutes in a dissolution test according to a Paddle Method.

Even though the above limitations are not taught, the examiner has reason to believe that these features are inherent. Because the examiner has no access to laboratory equipment, burden is put on the applicant to prove otherwise. When the reference discloses all the limitations of a claim except a property or function and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, the examiner can shift the burden of proof to the applicant as in In re Fitzgerald, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Because Lilliott et al describe a composition as a homogeneous admixture of both thiazolidinedione and metformin hydrochloride, it is assumed that the coefficient of variation of the insulin sensitizer would be the same as stated in claim 7. By mixing the

active ingredient and insulin sensitizer thoroughly, the prior art anticipates that each ingredient is uniformly dispersed.

In addition, it is assumed that the composition in Lilliott et al will perform the same as the instant claims in the dissolution test according to the Paddle Method. Since the conditions of this test are very specific and the examiner has no access to laboratory equipment, burden is put on the applicant to prove otherwise.

Furthermore, qualities associated with the hardness of a tablet are common standards in the pharmaceutical field and a tablet should be able to withstand breaking during the packaging and delivering process. Lilliott et al does not teach any characteristic associated with the hardness of the tablet. Thus, it is assumed that the hardness in Lilliott et al is the same as stated in claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lilliott et al (WO 01/35941) and further in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204).

Claims 4-6 are drawn to a solid preparation having an active ingredient with a ratio of median size thereof to the median size of an insulin sensitizer of 0.5 to 15. The active ingredient is preferably a biguanide that is metformin hydrochloride.

Determining the scope and contents of the prior art.

Lilliott et al teach a solid oral dosage comprising an insulin sensitizer and metformin hydrochloride that are uniformly dispersed (see above rejection).

Ascertaining the differences between prior art and instant claims.

Lilliott et al does not teach the ratio of median size between the active ingredient and insulin sensitizer.

Resolving the level of ordinary skill in the pertinent art.

To those skilled in the art, the influence of particle size affects whether or not the ingredients are uniformly dispersed. According to Zhuang et al, relatively similar smaller sized particles are very important for ensuring the uniformity of a tablet. Therefore, one of ordinary skill would be motivated from the teachings of Zhuang et al to optimize the ratio of median size between the active ingredient and insulin sensitizer.

Thus, the instant claims are *prima facie* obvious over the teaching of the prior art.

Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cutie et al (WO 01/82875) and further in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204).

Claims 13-14 are drawn to a solid preparation containing pioglitazone hydrochloride and metformin hydrochloride with a ratio of median size of metformin hydrochloride to a median size of pioglitazone hydrochloride of 0.5-15. In addition, the preparation is film-coated.

Determining the scope and contents of the prior art.

Cutie et al teach a combination drug product with metformin and pioglitazone hydrochloride employed to treat diabetes mellitus (abstract). According to Cutie et al, the core formulation of the present invention is preferably fabricated by compression into a tablet (pg. 6, lines 15-16). In addition, the core formulation may be coated with sugar, shellac, or other enteric coating agents (pg. 7, lines 9-11).

Ascertaining the differences between prior art and instant claims.

Cutie et al does not teach the ratio of median size between pioglitazone hydrochloride and metformin hydrochloride.

Resolving the level of ordinary skill in the pertinent art.

To those skilled in the art, the influence of particle size affects whether or not the ingredients are uniformly dispersed. According to Zhuang et al, relatively similar smaller sized particles are very important for ensuring the uniformity of a tablet. Therefore, one of ordinary skill would be motivated from the teachings of Zhuang et al to optimize the ratio of median size between pioglitazone hydrochloride and metformin hydrochloride.

Thus, the instant claims are *prima facie* obvious over the teaching of the prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL WELTER whose telephone number is (571) 270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Janet Andres or Cecilia Tsang can be reached at (571) 272-0867 or (571)272-0562 respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 4131

REW